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# Host-directed therapies for multidrug resistant tuberculosis

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## ABSTRACT

Tuberculosis (TB) causes 1.3 million deaths annually. There are 0.5 million cases of multidrug resistant TB (MDR-TB) and the number of cases is rising globally. The current status quo of the lengthy treatment duration and poor treatment outcomes associated with MDR/ extensively drug-resistant TB, and those with comorbidity of TB with human immunodeficiency virus and noncommunicable diseases in sub-Saharan Africa is unacceptable. The TB drug pipeline remains sparse. New innovations for shortening the duration of therapy and improving treatment outcomes (cure and long-term functional disability due to lung damage) are urgently required. A wide range of host-directed therapies (HDT) are now available which require evaluation as adjuncts to current TB drug treatment. Examples are:

- (1) Repurposed drugs:
  - Analgesics/nonsteroidal anti-inflammatory drugs (cyclooxygenase-2 inhibitors, e.g., ibuprofen).
  - Cholesterol-lowering drugs (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, e.g., simvastatin).
  - Asthma drugs (leukotriene synthesis inhibitors, e.g., zileuton).
  - Diabetes drugs (reactive oxygen species removal and increased CD8+ T-cell responses (e.g., metformin).
  - Anticonvulsants (inhibition of histone deacylation, e.g., valproic acid).
- (2) Cellular therapy: using the patient's own bone marrow-derived stromal cells.
- (3) Immune therapies: for example, anti-interleukin-6/interleukin-6 receptor monoclonal antibody.
- (4) Therapeutic vaccines: protein vaccines (e.g., granulysin), DNA vaccines, environmental mycobacteria vaccines (e.g., *Mycobacterium vaccae*, *Mycobacterium indicus pranii*).
- (5) Micronutrients: for example, Vitamin D, zinc, probiotics, and so forth.

The Host-directed Therapies Network consortium of 64 partners was launched in Cape Town after a meeting hosted by the South African Medical Research Council in April 2015. This network (which is open to anyone interested) plans to take forward a wide range of HDTs in randomized, placebo-controlled clinical trials as adjuncts to current TB treatment regimens with the aims of:

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- (1) Shortening the duration of treatment for drug-sensitive TB and MDR-TB.
  - (2) Improving treatment outcomes (mortality/morbidity) for MDR/extensively drug-resistant TB patients.
  - (3) Improving lung function and preventing lung damage so that the patient can return to gainful employment after treatment.
  - (4) Improving treatment outcomes for clinical presentations associated with tissue injury:
    - (i) Miliary TB (including TB meningitis and TB pericarditis).
    - (ii) Immune reconstitution inflammatory syndrome.
  - (5) Improving treatment outcome of TB and/or human immunodeficiency virus-positive individuals with comorbidities such as noncommunicable diseases (e.g., diabetes, liver disease, and cardiac disease), and cancers.
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### Conflicts of interest

The authors have nothing to disclose.